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Advances in Neuroimaging of Childhood Autism Spectrum Disorders

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Abstract: ***Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders that start in early development, with high disability rate, difficult to cure, and can last until adolescence and adulthood. Therefore, early diagnosis of ASD and early intervention are of great significance to its improvement and prognosis. Neuroimaging can provide the basis for early diagnosis and early intervention of ASD by evaluating the neuropathological changes in brain structure and function, white matter fiber bundle connections and brain tissue metabolism of children with ASD.***

Keywords: Autism, Early diagnosis, Neuroimaging, Magnetic resonance imaging.

1. Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders that begin in the early stages of development and are characterized by impairments in social interaction, communication disorders, narrowed interests, and stereotypical and repetitive behaviors, mostly accompanied by varying degrees of intellectual, perceptual, and emotional impairments [1-2]. Rates are a major global public health concern [3-5]. According to data released by the Centers for Disease Control and Prevention (CDC), the prevalence of childhood autism spectrum disorders (ASD) in the U.S. has continued to increase from 2018 to 2020, with its prevalence rate going from 1/54 to 1/44 in just two years, and the latest data shows that the 2020 The prevalence of ASD among 8-year-old children in the United States will be 1/36 in 2020, while the prevalence of ASD among children in China is also increasing year by year, and they are affected by ASD to varying degrees, as mentioned in the Specification for Autism Screening and Intervention Services for Children 0-6 Years of Age (for Trial Implementation) released by the General Office of the National Health and Health Commission of China in 2022, which states that "the prevalence of autism among children in China is about 0.7%". Research has confirmed that children with ASD have plasticity in their early neurological structures, and early diagnosis and effective interventions are of great significance to the improvement and prognosis of children with ASD. Neuroimaging technology, because of its unique advantages in exploring the structure and function of the brain, has been used by many scholars in the diagnosis of ASD, which can show the pathophysiological changes of ASD by evaluating the morphology of the brain structure, the integrity of the white matter fiber tracts, and the metabolism of the substances, and provide a more reliable and objective basis for the early clinical diagnosis of ASD. (Figure 1 and Figure 2)

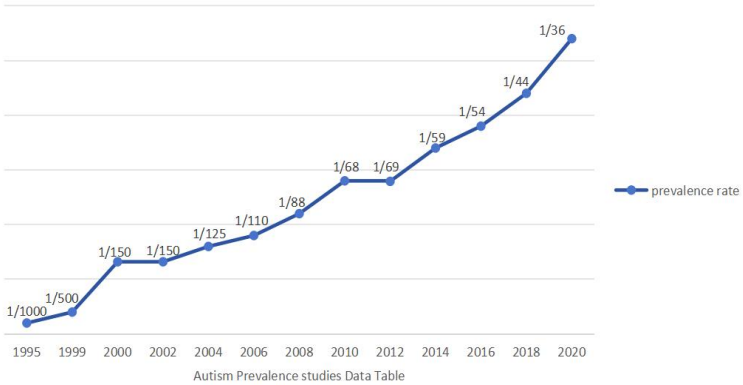

Figure 1: Identified Prevalence of Autism Spectrum Disorder (ADDM Network 2000-2020 Combining Data from All sites)

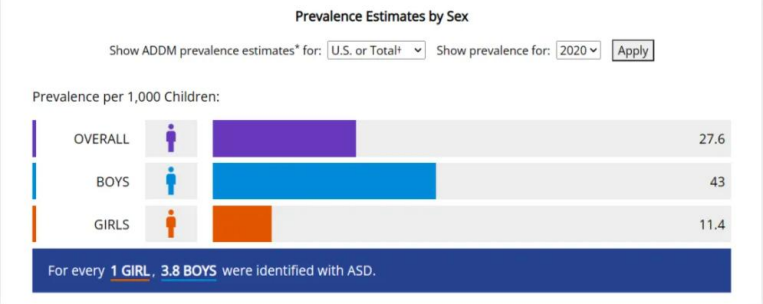

Figure 2: Prevalence Estimates by Sex

2. ASD Overview

The cause and pathogenesis of ASD are still unclear, scholars at home and abroad have explored the etiology of ASD from epidemiology, genetics, immunology, maternal and perinatal biology, etc, and most of them believe that it is caused by the interaction between genetic factors and environmental factors, abnormal immune function, abnormal neuronal development, imbalance of the ratio of intestinal bacteria and other high-risk factors. ASD has a complex pathogenesis, and the current exploration of the pathogenesis mainly focuses on synaptic developmental disorders, loop function defects, and changes in the gut-brain axis and related signaling molecular pathways. The pathogenesis of ASD is complex, and the current research on its pathogenesis mainly focuses on synaptic developmental disorders, loop function defects, changes in the gut-brain axis, and changes in related signaling molecular pathways [6]. Because the etiology and pathogenesis of ASD are still unclear, its diagnosis and treatment are difficult.

At present, the clinical diagnosis of ASD is mainly based on the subjective assessment of behavioral manifestations and symptoms of children with ASD through various scale tools, which is somewhat experience-dependent. Neuroimaging research [7-9] elaborates the neural mechanism of ASD from the aspects of brain microstructure, functional imaging, and neurometabolism, and finds that there are abnormalities in the cerebellum in terms of microstructure, function, neurotransmitters, and substance metabolism, and these abnormalities are related to the symptoms of ASD, which help us to better understand the pathologic mechanism of ASD. Neuroimaging can safely, noninvasively, and objectively detect the alterations of brain structure and function in children with ASD, and has a wide range of prospects for application in ASD research, providing objective imaging evidence for the diagnosis of ASD [10].

3. Structural Magnetic Resonance Imaging (sMRI)

High-resolution 3D T1 images were acquired by sMRI, and brain volumetric measurements, brain surface folds, etc. were investigated by post-processing techniques. Commonly used analysis methods include voxel-based morphological analysis and surface-based morphological analysis [11]. Voxel-based morphological analysis reflects the changes in brain volume in children with autism, and there are early differences in the neural growth trajectories of children with ASD, whose brains seem to grow faster than normally developing brains, with an increase in brain volume of about 10% [12]. Chu Kangkang et al. [13] found that the volume of brain white matter in the frontal and temporal lobes of children with ASD was increased by longitudinal comparative analysis, and these brain regions were mainly related to social-emotional and language expression, etc. It was hypothesized that the changes in these regions might be the underlying pathological basis of social and cognitive impairments in children with ASD [14]. A meta-analysis suggested that children with ASD have increased gray matter volume in several brain regions, including the posterior central gyrus and superior temporal gyrus, and the changes in gray matter volume were significantly correlated with the patients' mean IQ, speculating that these changes may contribute to mental retardation in children with ASD [15]. Morphological analysis based on the surface layer mainly reflects microstructural changes, such as the degree of brain surface folds, cortical thickness, etc. Kohli et al. [16] found that the number of cortical folds in certain cortical regions tended to be elevated in children with ASD, but decreased with age, which may be related to early brain overdevelopment in children with ASD. It was found that the cortex of the striatum, frontal cortex and temporal cortex and other emotion and cognition-related brain regions in children with ASD were thickened compared with that of normal children [17-18], suggesting that the thickening of the brain cortex may have a certain relationship with the occurrence of ASD. In conclusion, sMRI can observe the changes in the brain structure of children with ASD mainly through the changes in brain volume and the fine structure of brain surface folds, and then assist in the clinical diagnosis of ASD.

4. Functional Magnetic Resonance Imaging (fMRI)

fMRI is a blood oxygenation level dependent (BOLD) functional brain imaging, which is based on the principle of measuring changes in the degree of oxygenation in the local cerebral blood flow, thus indirectly reflecting the functional activity of brain regions [19]. The study methods of fMRI include the resting state and the task state, whereas the former only requires the subject to be in a quiet state during the scanning process. The former requires only a quiet state during the scanning process, while the latter requires the subject to cooperate in accomplishing a certain task. Several studies have shown that ASD has abnormal neural activity in brain regions associated with social functioning, including the medial prefrontal lobe, superior temporal sulcus, amygdala, and fusiform gyrus. [20]. Impaired facial expression processing is one of the important manifestations of social impairment in ASD, a task state fMRI study found that under conditions of facial expression stimulation, adults with ASD have reduced activation in several social brain regions such as the amygdala [21]. Odriozola et al. [22] used the amygdala as a region of interest, and found that functional connectivity between the amygdala and the medial prefrontal lobe is diminished in resting-state children and adolescents with ASD, whereas weaker functional connectivity in adolescents with ASD than in children with ASD, suggesting that abnormal amygdala-frontal functional connectivity may be an underlying mechanism of socioemotional impairment in ASD and may differ between age groups. In recent years, with the continuous improvement of fMRI research methods, more and more researchers have proposed that ASD may have abnormal neural activity in large-scale functional networks rather than individual brain regions. The default mode network (DMN) is the most studied brain network in ASD, and its major nodes are located in the posterior cingulate/precuneus cortex. The DMN is active in the resting state and plays an important role in the theory of mind (ToM) [23], and deficits in the ToM are one of the major hypotheses of social communication deficits in ASD. [24] Cherkassky et al. [25] and Funakoshi et al. [26] reported reduced functional connectivity of the DMN in the resting state in adults and children with ASD, respectively. Lombardo et al. [27] found that children with ASD with impaired social visual engagement had reduced functional connectivity between the

DMN and the visual brain network, which was associated with more severe social communication deficits, suggesting that abnormalities of functional connectivity of the DMN may be a potential mechanism for social impairment in ASD. potential mechanism for social impairment in ASD. Some fMRI studies have explored brain functions associated with the symptoms of repetitive and repetitive behaviors (RRB) in ASD. Researchers have proposed that RRB in ASD may be associated with abnormalities in cortico-basal ganglia neural circuits [28], which is consistent with structural imaging findings. Akkermans et al. [29] found that the strength of functional connectivity between the striatum to premotor cortex and the middle frontal gyrus was positively correlated with the severity of RRB in children and adolescents with ASD. A national study found enhanced localized functional connectivity from the left inferior temporal gyrus to the left fusiform gyrus in 6- to 18-year-olds with ASD and correlated with higher RRB scores [30]. In conclusion, several studies have found abnormalities in brain function in ASD, especially in brain regions such as the prefrontal lobe, amygdala, and striatum that may be involved in core symptoms, and functional connectivity abnormalities in the DMN have also been frequently reported in studies. fMRI with high spatial resolution can measure neural activity in ASD at rest or during tasks, which is helpful in detecting abnormalities in functional connectivity or activation state of the ASD brain. However, its limitation is that head movements, breathing, etc. tend to cause motion artifacts, and it is relatively difficult to cooperate in young children with ASD.

5. Diffusion-tensor Imaging (DTI)

DTI is currently the only non-invasive in vivo quantitative assessment of the integrity and orientation of cerebral white matter fiber tracts, which is sensitive to the diffusion of water molecules in biological tissues, and is able to visualize the macroscopic and microscopic structure of cerebral white matter fiber tracts, as well as the conduction pathways of the white matter fiber tracts and their developmental changes. [11, 31] It is one of the most effective methods for studying structural connectivity of the cerebral white matter at the present time. Steinbrink et al. [32] found that partial anisotropy (FA) was reduced in the white matter near the ventral prefrontal cortex, anterior cingulate gyrus, and temporoparietal junction in the ASD group, and other clusters of reduced FA could be seen bilaterally in the temporal lobes close to the amygdala, the corpus callosum, and bilaterally adjacent to the superior temporal sulcus in the ASD children. In recent years, many scholars [33-36] have also found decreased FA in the white matter of the brain in children with ASD, including the arcuate fasciculus, cingulate fasciculus, superior longitudinal fasciculus, internal capsule, and corpus callosum, etc. It is hypothesized that the myelin sheaths and axons in the neural pathways associated with ASD are smaller in size and lower in density, leading to defects in the integrity of the axons and a restriction in the presence of myelin, which then causes the emergence of the corresponding clinical symptoms in children with ASD. Numerous studies have suggested that white matter structure seems to be particularly affected in the development of children with ASD, showing reduced myelin formation and lower FA values, suggesting a unique neurodevelopmental pattern in ASD, and that this underlying structural difference may affect learning and social communication abilities. DTI, by evaluating the integrity of the cerebral white matter fiber tracts and changes in the related parameters, can observe whether and to what extent the fiber tracts are damaged, and may provide new insights into the diagnosis of ASD. The DTI may provide new insights into the diagnosis of ASD.

6. Wrap-up

ASD is a complex neurodevelopmental disorder, the etiology and pathogenesis of which are still unclear, and its research has always been a hot and difficult topic. At present, scholars recognize that early intervention for ASD patients is of great significance to their prognosis, and there is an urgent need for more effective methods for early diagnosis of ASD patients. The development and application of neuroimaging technology has greatly expanded our understanding of the neural mechanisms of ASD. As mentioned above, previous studies have revealed alterations in brain structure and brain function in ASD, and these alterations may be the underlying mechanisms for the core symptoms of ASD. Current neuroimaging studies have achieved better results in reflecting the neuropathologic changes of ASD, but correlation studies with clinical symptoms and genetics are still insufficient, and pure neuroimaging manifestations are not yet convincing as a basis for diagnosing ASD. In the future, imaging genomics, genomics, and artificial intelligence are needed to provide a more reliable and objective basis for clinical ASD diagnosis at the macro and micro levels.

Due to the complexity of ASD disease, a single technique has certain limitations, and in the future we need to combine a variety of imaging techniques to conduct multimodal studies of ASD. In addition, the imaging findings of ASD disease are highly heterogeneous, indicating that the disease is likely to be composed of different subtypes, and in the future we need to carry out a large-sample-size, multicenter study to further classify ASD using multimodal neuroimaging which provides more valuable medical imaging basis for early diagnosis and rehabilitation treatment.

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